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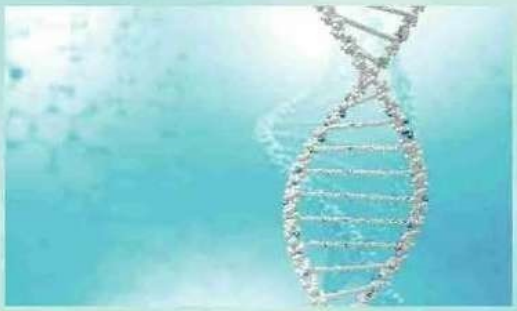

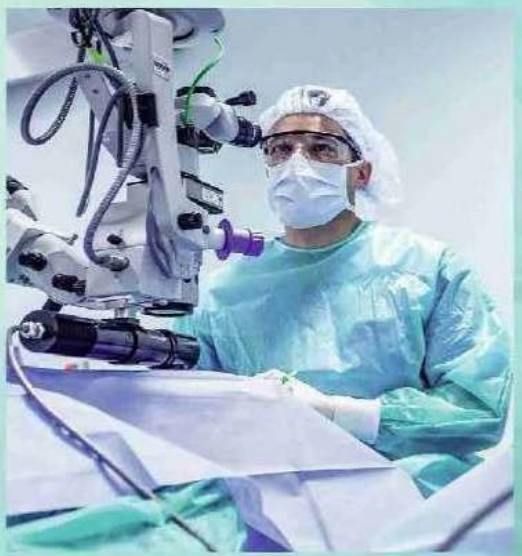

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E: ndmuz@mail.ru
Тел: +99890 8061882

ТИББИЁТДА ЯНГИ КУН

НОВЫЙ ДЕНЬ В МЕДИЦИНЕ

NEW DAY IN MEDICINE

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MODERN CONCEPTS OF KIDNEY DAMAGE IN PATIENTS WITH SYSTEMIC SCLERODERMA *(literature review)*

[1]Abdullaeva Umida Kurbanovna, https://orcid.org/0000-0002-1495-3668
[2]Nabieva Dildora Abdumalikovna, https://orcid.org/0009-0007-0177-0540
[3]Yusupov Ilkhom Kobulzhonovich https://orcid.org/0009-0008-5738-0565

[1]Bukhara State Medical Institute named after Abu Ali ibn Sina Uzbekistan Bukhara, A.Navoi st. 1 Tel: +998(65) 223-00-50 e-mail: info@bsmi.uz
[2]Tashkent Medical Academy 100109, Tashkent, Uzbekistan Farabi Street 2. Tel: +99878 1507825; E-mail: info@tma.uz
[3]Rheumatologist of the private clinic "Premium medical", Uzbekistan Fergana, st. Marifat 23 Tel: +998-73-244-22-13 https://fergana.clinics.uz

✓ ***Resume***

Systemic sclerosis, or systemic scleroderma (SSD), is an autoimmune disease of connective tissue, the main clinical signs of which are caused by widespread microcirculation disorders, fibrosis of the skin and internal organs. According to morphological studies, 80% of patients with SSD have kidney changes, including those not associated with rheumatic diseases. While the prevalence of sclerodermic renal crisis is currently estimated at 2-5%, an asymptomatic decrease in renal function ("mute uremia") due to the presence of multimorbid and comorbid pathology is much more often noted. Its frequency in patients with SSD can reach 55%. The fact of the presence of autoimmune connective tissue disease itself can be considered as a risk factor for kidney damage. The fifteen–year survival rate of patients with CVD without kidney damage is 72%, in the presence of kidney damage - no more than 13%. The presence of proteinuria in patients with SSD is one of the most significant independent risk factors for death (the relative risk is 3.34), leaving far behind such canonical risk factors as pulmonary arterial hypertension, pulmonary restriction (the ratio of forced expiratory volume in 1 s and forced vital capacity of the lungs <80%), respiratory failure (III and class IV according to NYHA), as well as a decrease in the diffusion capacity of the lungs and a high skin score.

Keywords: systemic scleroderma; sclerodermic renal crisis; vascular endothelial dysfunction; chronic sclerodermic nephropathy; nonimmune factors of nephropathy progression; chronic kidney disease.

СОВРЕМЕННЫЕ ПРЕДСТАВЛЕНИЯ О ПОРАЖЕНИЙ ПОЧЕК У БОЛЬНЫХ СИСТЕМНОЙ СКЛЕРОДЕРМИЕЙ (ОБЗОР ЛИТЕРАТУРЫ)

[1]Абдуллаева Умида Курбановна https://orcid.org/0000-0002-1495-3668
[2]Набиева Дилдора Абдумаликовна https://orcid.org/0009-0007-0177-0540
[3]Юсупов Илхом Кобулжонович https://orcid.org/0009-0008-5738-0565

[1]Бухарский государственный медицинский институт имени Абу Али ибн Сины, Узбекистан, г. Бухара, ул. А. Навои. 1 Тел: +998 (65) 223-00-50 e-mail: info@bsmi.uz
[2] Ташкентская Медицинская Академия (TMA) Узбекистан, 100109, Ташкент, Алмазарский район, ул. Фароби 2, тел: +99878 1507825, E-mail: info@tma.uz
[3]Ревматолог частной клиники «Premium medical», Узбекистан Фергана, ул. Маърифат 23 тел: +998-73-244-22-13 https://fergana.clinics.uz

✓ ***Резюме***

Системный склероз, или системная склеродермия (ССД), является аутоиммунным заболеванием соединительной ткани, основные клинические признаки которого обусловлены распространенными нарушениями микроциркуляции, фиброзом кожи и

внутренних органов. По данным морфологических исследований, у 80% пациентов с ССД имеются изменения в почках, в том числе не связанные с ревматическими заболеваниями. В то время как распространенность склеродермического почечного криза в настоящее время оценивается в 2-5%, гораздо чаще отмечается бессимптомное снижение функции почек ("немая уремия") из-за наличия мультиморбидной и сопутствующей патологии. Его частота у пациентов с ССД может достигать 55%. Сам факт наличия аутоиммунного заболевания соединительной ткани можно рассматривать как фактор риска повреждения почек. Пятнадцатилетняя выживаемость пациентов с ССЗ без повреждения почек составляет 72%, при наличии повреждения почек - не более 13%. Наличие протеинурии у пациентов с ССД является одним из наиболее значимых независимых факторов риска смерти (относительный риск составляет 3,34), оставляя далеко позади такие канонические факторы риска, как легочная артериальная гипертензия, ограничение легочной функции (соотношение объема форсированного выдоха за 1 с и форсированной жизненной емкости легких <80%), дыхательная недостаточность (III и IV класс по NYHA), а также снижение диффузионной способности легких и высокий кожный балл.

Ключевые слова: системная склеродермия; склеродермический почечный криз; дисфункция сосудистого эндотелия; хроническая склеродермическая нефропатия; неиммунные факторы прогрессирования нефропатии; хроническая болезнь почек.

TIZIMLI SKLERODERMIYA BILAN OG'RIGAN BEMORLARDA BUYRAK SHIKASTLANISHI HAQIDAGI ZAMONAVIY G'OYALAR *(Adabiyotlar sharhi)*

[1]Abdullaeva Umida Kurbanovna, https://orcid.org/0000-0002-1495-3668
[2]Nabieva Dildora Abdumalikovna, https://orcid.org/0009-0007-0177-0540
[3]Yusupov Ilkhom Kobulzhonovich https://orcid.org/0009-0008-5738-0565

[1]Abu Ali ibn Sino nomidagi Buxoro davlat tibbiyot instituti, O‘zbekiston, Buxoro, st. A. Navoiy. 1
Tel: +998 (65) 223-00-50 e-mail: info@bsmi.uz
[2]Toshkent tibbiyot akademiyasi, 100109 Toshkent, O‘zbekiston Farobiy ko’chasi 2,
Tel: +998781507825 E-mail: info@tma.uz
[3]“Premium medical” shaxsiy klinikasi revmatologi, O'zbekiston Farg'ona sh. Ma'rifat 23 Tel: +998-73-244-22-13 https://fergana.clinics.uz

✓ ***Rezyume***

Tizimli skleroz yoki tizimli sklerodermiya (TSD) biriktiruvchi to'qimalarning autoimmin kasalligi bo'lib, uning asosiy klinik belgilari mikrosirkulyatsiyaning keng tarqalgan buzilishlari, teri va ichki organlarning fibrozidan kelib chiqadi. Morfologik tadqiqotlarga ko'ra, TSDli bemorlarning 80 foizida buyraklarda o'zgarishlar, shu jumladan revmatik kasalliklar bilan bog'liq bo'lmagan o'zgarishlar mavjud. Sklerodermik buyrak inqirozining tarqalishi hozirda 2-5% deb taxmin qilinayotgan bo'lsa-da, multimorbid va komorbid patologiyaning mavjudligi sababli buyrak funktsiyasining simpromsiz pasayishi ("soqov uremiya") tez-tez uchraydi. TSD bilan og'rigan bemorlarda uning chastotasi 55% gacha bo'lishi mumkin. Autoimmun biriktiruvchi to'qima kasalligi mavjudligi faktini buyrak shikastlanishi uchun xavf omili sifatida ko'rish mumkin. Buyrak shikastlanishisiz yurak qon tomir kasalliklari bilan og'rigan bemorlarning o'n besh yillik omon qolish darajasi 72% ni tashkil qiladi, agar buyrak shikastlangan bo'lsa - 13% dan oshmaydi. TSD bilan og'rigan bemorlarda proteinuriyaning mavjudligi o'lim uchun eng muhim mustaqil xavf omillaridan biridir (nisbiy xavf 3,34), o'pka arterial gipertenziyasi, o'pka funktsiyasining cheklanishi, nafas olish yetishmovchiligi (III va NYHA bo'yicha IV sinf), shuningdek o'pkaning diffuz qobiliyatining pasayishi va terining yuqori shikastlanish kabi kanonik xavf omillarini ortda qoldiradi.

Kalit so'zlar: tizimli sklerodermiya; sklerodermali buyrak inqirozi; qon tomir endotelial disfunktsiya; surunkali sklerodermali nefropatiya; nefropatiya rivojlanishining immun bo'lmagan omillari; surunkali buyrak kasalligi.

Relevance

Systemic sclerosis, or systemic scleroderma (SSD), is an autoimmune disease of connective tissue, the main clinical signs of which are caused by widespread microcirculation disorders, fibrosis of the skin and internal organs [1].

Back in 1863, H. Auspitz [2] first described as a casuistic case of progressive renal failure in a patient with SSD, but at that time the author did not assume that there was a connection between these two conditions.

The kidneys are often involved in the pathological process in rheumatic diseases (RH). In most cases, kidney damage is asymptomatic and its detection requires the use of additional instrumental and laboratory diagnostic methods [3].

According to morphological studies, 80% of patients with SSD have kidney changes, including those not associated with RH [4]. Medications used for the treatment of RH, for the most part, having nephrotoxic properties, also add variety to the "kaleidoscope" of kidney pathology.

Until the end of the 70s of the last century, kidney damage in the form of a "true sclerodermic kidney", observed in 12-18% of patients, was the leading cause of death in patients with SSD [5].

And 40 years later, the fundamental work carried out under the leadership of N.G. Guseva, V.A. Nasonova and I.E. Tareeva [6] is still of interest, in which a decrease in glomerular filtration rate (GFR) in 65% of cases was noted in patients with SSD in the absence of clinical symptoms of kidney damage. Morphological examination of the renal biopsy revealed changes in 100% of cases. The authors paid special attention to the diversity of the histological picture of 25 renal biopsies: in 6 cases, a true sclerodermic kidney was detected, in 15 – membranoproliferative or proliferative fibroplastic glomerulonephritis with varying degrees of severity of glomerular sclerosis; in two – mesangial type of glomerulonephritis and in two more cases – amyloidosis. In their conclusions, relying on their own data and data obtained in the works of other authors (overwhelmingly based on the use of accurate diagnostic methods both in patients with SSD and on experimental models), the researchers emphasized the nosological diversity of kidney damage options in patients with SSD, including without an etiological connection with the disease itself.

Progress in the treatment of sclerodergmic renal crisis (SRC) associated with the initiation of angiotensin converting enzyme (ACE) inhibitors has led to a significant decrease in clinicians' interest in the problem of kidney damage in patients with SSD. Currently, most of the works dealing with the problem of kidney damage in patients with DM are focused on assessing the frequency, prognosis, and risk factors of SRC.

At the same time, the views expressed several decades ago by N.G. Guseva and V.A. Nasonova on the problem of the diversity of kidney pathology in patients with SSD are reflected today. So, V.K. Shanmugam and V.D. Steen [7] identified the following variants of kidney damage in patients with DM: 1) SRC, 2) normotensive SRC (nSRC), 3) associated with antineutrophilic ancytoplasmic antibodies (ANCA) glomerulonephritis and vasculitis, 4) nephropathy associated with antiphospholipid syndrome (AFS), 5) D-penicillamine nephropathy, 6) isolated decrease in GFR, 7) decrease in the functional reserve of the kidneys, 8) microalbuminuria and proteinuria, 9) sclerodermic vasculopathy, manifested by changes in the indices of renal resistance and endothelial markers.

This classification covers both nosological units and individual markers of renal damage. It seems to us expedient, based on the etiopathogenetic differences of kidney damage in patients with SSD, to distinguish three large groups of nephropathies, including in the classification a previously undescribed chronic sclerodermic kidney lesion: nephropathy caused by vascular endothelial dysfunction (ED).

Nephropathies associated with scleroderma scleroderma renal crisis

Such a formidable variant of kidney damage in SSD has long been known as SRC, characterized by the development of acute renal failure (ARF) and, as a rule, moderate or severe arterial hypertension (AH) with hyperreninemia [10]. The terms "true sclerodermic kidney" and "acute sclerodermic nephropathy" are also used to describe it. For a long time, SRC was the most common cause of death of patients with SSD.

The frequency of development of SRC until the end of the 70s of the last century reached 12-18% [5]. The turning point was the use of ACE inhibitors in the treatment of SRC, which allowed to reduce the overall annual mortality rate of DM patients from 76 to less than 15% [11]. However, the mortality rate in the group of patients with SRC remains unacceptably high – after 10 years, only one in two

remains alive [5]. Currently, since the beginning of the "era of ACE inhibitors", according to the analysis of the EUSTAR database (European database of scleroderma tests and research) The European Antirheumatic League (EULAR), the prevalence of SRC is less than 5% among patients with diffuse form of SSD and 2% among patients with limited form of SSD [12].

In 1952, H.C. Moore and H.L. Sheehan [13] for the first time isolated and described the changes characteristic of the SRC. The development of SRC is based on renal vasospasm ("renal Raynaud's syndrome"), which leads to damage to endothelial cells, proliferative vasculopathy of mainly arc and intralobular renal arteries with fibrin thrombi and fibrinoid necrosis of these vessels [14]. In the future, fibrosis and compaction of the extracellular matrix of the glomeruli and tubules of the interstitium, mucoid swelling of the intima of the vessels and concentric hypertrophy of the intralobular arteries of the "bulbous husk" type are formed [15].

Common clinical symptoms of SRC are malignant hypertension, headache, fever, and weakness, shortness of breath, proteinuria (to a neurotic level), hematuria, hypertensive retinopathy and encephalopathy. Hypertension is hyperrenic in nature, which is associated with the high efficiency of ACE inhibitors in such patients. It should be emphasized that hyperreninemia, as a rule, is not detected before the development of SRC and is not a predictor of it, as demonstrated in a large prospective study involving 57 patients with SRC [17]. Hemolytic anemia and thrombocytopenia are quite common, reaching 65 and 50% of cases, respectively [18]. Approximately half of patients with SRC show signs of thrombotic microangiopathy (TMA) [19]. It is possible to develop acute cardiorenal syndrome (type 1, type 3 or type 5), manifested by pulmonary edema, congestive heart failure, oligo- or anuria [20]. Rarely, the diagnosis of SRC is associated with diffuse hemorrhagic alveolitis and TMA [21]. Unlike idiopathic TTP, with TMA associated with SSD, there is no pronounced deficiency of ADAMTS 13 [22], and the formation of blood clots occurs not in the capillaries of the glomeruli, but in small renal vessels [23]. In approximately 20% of patients with SRC, its development precedes the diagnosis of SSD [16].

Despite the active study of the SEC, there are still no uniform standardized criteria for its diagnosis. As a rule, normotensive and hypertensive SRC are distinguished. A group of experts of the International Society for the Study of Sclerodermic Renal Crisis (ISRCS) [24] proposed to diagnose a hypertensive variant of SRC in the presence of the following criteria:

1. First-time hypertension, defined as:

a) systolic blood pressure (SBP) ≥140 mm Hg;

b) diastolic blood pressure (DBP) ≥90 mm Hg;

c) an increase in SBP by 30 mm Hg or more;

d) an increase in DAP by 20 mmHg or more.

2. One of the following five signs:

a) an increase in serum creatinine by 50% or more relative to the basal level or 120% or more of the upper limit of the norm for this laboratory;

b) proteinuria 2+ or more;

c) hematuria 2+ and more or more than 10 cells in the field of vision;

d) tromocytopenia less than 100 • 109/l;

e) hemolytic anemia (including the detection of fragments of erythrocytes, schistocytes or reticulocytosis).

The development of hypertensive encephalopathy was also considered as a possible criterion.

In 10-20% of cases, nSPC is diagnosed [18], characterized by a high risk of developing terminal renal failure and death [25]. However, the criteria for the diagnosis of nSRC are non-specific and differ from one author to another [15, 16, 24, 26]. Common to all the proposed criteria is the presence of hemolytic anemia, hematuria, proteinuria, thrombocytopenia. In addition, various authors suggest including the dynamics of creatinine levels, the presence of pulmonary edema, oliguria and anuria among the criteria.

Conducting a kidney biopsy is not considered as a mandatory component of confirming the diagnosis. Given the non–specificity of the criteria used, it can be assumed that under the diagnosis of SRC, and especially nSRC, other variants of kidney damage may be hidden in patients with SSD. And the high mortality rate of such patients is due to the difficulties of diagnosis and, as a consequence, erroneous approaches to therapy.

Identification and monitoring of patients with SRC and those at risk of developing SRC is of key importance in reducing mortality and the risk of irreversible terminal renal failure [27, 28].

The diffuse form of SSD is considered as one of the main risk factors for SRC. Experts agree that the rapid progression of skin sclerosis is an independent predictor of the development of SRC. In most patients with a diffuse form of SSD, SRC develops in a period of 7.5 months to 4 years [14].

In four different retrospective studies involving 544 patients with SSD, an association of the development of SRC and the use of steroids in the treatment was revealed [31-34]. In a case–control study [32], it was demonstrated that during the 6 months preceding the development of SRC, 36% of patients received prednisone (or analogues) at a dose of 15 mg/day or more, compared with 12% in the control group [odds ratio (OR) 4.4; p=0.001]. In the same study, it was noted that the new appointment of low doses of steroids, taking nonsteroidal anti-inflammatory drugs, BCI, ACE inhibitors do not increase the risk of developing SRC.

Antibodies to RNA polymerase-3 (when determined using ELISA) are highly specific for the diffuse form of SSD, and 24-33% of patients positive for these antibodies develop SRC [35].

An increase in the level of sCD147, an extracellular matrix metalloproteinase inhibitor, which is a serum protein belonging to the immunoglobulin superfamily, is considered as a possible marker of an increased risk of developing SRC in patients with DM. In a study by K. Yanaba et al. [27] it was noted that in patients with elevated levels of sCD147 (ELISA) SRC developed more often than in patients with normal levels (13% and 0, respectively; p<0.05).

Genetic predisposition also matters: the carriage of HLA-DRB1*0407 (OR=3.21; p=0.013) and HLA-DRB1*1304 (OR=4.51; p=0.018) is an independent risk factor for the development of SRC [18].

Aggressive hypotensive therapy of SRC is the main method of preventing irreversible vascular damage. Lowering blood pressure (BP) should be achieved within 2-3 days, but without pronounced fluctuations in its level, preference is given to short-acting drugs. A sharp drop in blood pressure can lead to a significant decrease in renal perfusion and, as a consequence, acute tubular necrosis [19].

Despite the absence of randomized controlled trials, EULAR experts consider it necessary to use ACE inhibitors in the treatment of SRC [20]. BAR are less effective than ACE inhibitors, which is probably due to the absence of a bradykinin-potentiating effect [21]. If the effectiveness of ACE monotherapy is insufficient, it is necessary to add antihypertensive drugs of other groups to the treatment (BCI, moxonidine, nitroprusside, etc.). The use of non-selective beta-blockers should be avoided. It is important that the use of ACE inhibitors in the period preceding the development of SRC not only does not have a nephroprotective effect, but is also associated with a high risk of terminal renal failure and death of patients [14].

Some centers additionally recommended the use of iloprost, a stable analogue of prostacyclin with vasodilating and antiplatelet properties, in SPC. With intravenous use, iloprost increases the renal plasma flow, expanding the bringing and carrying arterioles [25].

There are separate clinical reports on the positive effect of endothelin receptor antagonists (ET) bosentan and sitaxentan on the restoration of renal function in patients with SSD, including those on hemodialysis, with the ineffectiveness of ACE inhibitors [29]. Currently, an open clinical trial is ongoing, the purpose of which is to study the effect of the ET receptor antagonist bosentan in patients with SRC. The use of anticoagulants in the treatment of SRC has not been studied.

An unfavorable prognosis of SRC is indicated by the occurrence of arrhythmia, myocarditis or pericarditis [14]. Poor prognostic factors of the outcome of SRC include an increase in the level of the N-terminal fragment of the cerebral natriuretic peptide (NP-proBNP) of more than 360 pg/ml (p=0.019) [13], and an increase in the level of NP-proBNP of more than 1494 pg/ml is highly correlated with the inevitability of hemodialysis (OR=70; p<0.005) [24].

About 25% of patients already need hemodialysis at the time of diagnosis of SRC, some of them subsequently recover renal function with continued ACE therapy. However, 40-66% of these patients require programmed hemodialysis or kidney transplantation. The average recovery time of renal function is 1 year, in the future its probability decreases and approaches zero after 3 years of replacement therapy [25]. Kidney transplantation can significantly improve the prognosis and survival of patients with SRC and end-stage renal failure. Due to the existing possibility of restoring renal function, the operation should be performed no earlier than 18 months after the development of SRC. Nevertheless, the frequency of repeated development of SRC in a kidney transplant (both living and cadaveric kidney) reaches 20-50% [21].

Isolated decrease in glomerular filtration rate

Based on numerous observations of patients with SSD, it can be argued that a significant decrease in GFR occurs already with subclinical kidney damage, and according to some authors, it can be detected in almost half of patients with SSD with formally normal blood creatinine levels [7]. And only in a few studies there is an opposite point of view. So, A. Scheja et al. [8] noted a decrease in GFR in a small number of patients with SSD – out of 451 patients, 39 (11%) with a limited form and 9 (8.6%) with a diffuse form of SSD. At the same time, a decrease in creatinine clearance was associated to a greater extent with the presence of hypertension and cardiac pathology.

It is well known that in clinical practice, clearance techniques for determining GFR have long given way to computational methods. Both in the general population and in patients with SSD, the GFR value calculated in the CKD-EPI equation turned out to be the closest to the results of GFR measurement using one of the reference techniques (EDTA clearance labeled with technetium-99m) [7]. Detection of a decrease in GFR at subclinical stages is important not only for determining the renal prognosis, but also for calculating the doses of medications, including antibiotics, immunosuppressants, the use of radiopaque substances and determining the prognosis of SSD in general. So, A. Campo et al. [9] demonstrated that a decrease in the calculated GFR (eGFR) <60 ml/min/1.73 m2 is associated with a threefold increase in mortality in patients with pulmonary hypertension and SSD. Subclinical kidney damage is usually characterized by slow progression of CKD [6]. A small number of patients with CVD reach the terminal stage of chronic renal failure (CRF). For example, according to the national register of Australia and New Zealand ANZDATA, for the period from 1963 to 2005, out of 40,238 patients with end-stage renal failure, only 127 patients (0.3%) had CKD as the cause. At the same time, based on data from the same register, B. Siva et al. [5] demonstrated that the average survival in patients with terminal CRF on the background of SSD was significantly lower than in patients with other causes of CRF (2.43 and 6.02 years, respectively). But spontaneous recovery of renal function in patients with SSD was much more common than in other nephropathies (10 and 1%, respectively; $p<0.001$). The presence of SSD turned out to be an independent and independent predictor of both "renal death" and restoration of organ function. Thus, the 5-year survival rate of a cadaveric and donor kidney kidney transplant was 53 and 100%, respectively, and was comparable with other causes of terminal CRF.

Decreased renal reserve

To assess the state of intrarenal hemodynamics in clinical practice, the method of determining the renal functional reserve (PFR) is used, which is a percentage increase in GFR in response to protein loading. A normal response to protein loading or the introduction of amino acids is considered to be an increase in GFR by 20-65% within 1.5–2 hours after the start of the test. A decrease in the glomerular filtration reserve is considered as an early sign of impaired renal filtration function. R. Livi et al. [10] examined 21 patients with SDS with normal renal function, as well as a control group (10 patients) after intravenous administration of an amino acid solution (Freamine III Baxter kit, 8.5% solution, which was administered at a rate of 4.16 ml/min for 2 hours). Before and after the administration of amino acids, GFR (using creatinine clearance), effective renal plasma flow (using paraaminohippuric acid clearance), and total renovascular resistance were measured in all patients. Initially, patients with SSD compared with the control had a lower effective renal plasma flow (403.5±43.8 and 496.4±71.3 ml/min; $p<0.0002$) and a higher level of total renovascular resistance (10,822±2044 and 8874±1639 din/s • cm5, respectively; $p<0.014$). The PFR in SSD was also significantly lower than in the control (+1.9±18.6 and +34.8±13.9%, respectively; $p<0.0002$). However, the response of patients with SSD to the introduction of an amino acid solution was different. The analysis of multiple regression revealed the greatest inverse dependence of the PFR on the level of mean blood pressure and baseline GFR ($R2=65\%$; $p<0.0001$). Thus, the defect of the PFR according to the results of the test with amino acids confirms the concept of the prevalence of vasoconstrictor factors in the kidney over vasodilating factors in patients with SSD. In the future, the same group of scientists continued dynamic monitoring of the parameters of renal function in patients with SSD for 5 years [21]. Five years later, GFR decreased more significantly in patients with reduced PFR (≥2 ml/min per year), and many patients from this group developed grade 1 or 2 hypertension. The authors suggested that the absence of normal PFR may be both an early sign of kidney damage in SSD, and an independent predictor of the development of renal failure and hypertension as a result of impaired endothelial response to vasodilating stimuli.

Conclusion

For the first time, the authors propose the concept of the existence and pathogenesis of chronic sclerodermic nephropathy, which is based on the phenomenon of vascular endothelial dysfunction, formed in various structural components of the nephron and the kidney as a whole. In these scientific studies that we have analyzed, disorders at the genetic level are not fully covered, so we think that it is this part of the problem that needs to be researched in more depth in our opinion.

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